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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/770,601	01/26/2001	Myra A. Lipes	10276-015002	6880

26161 7590 10/10/2003

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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/770,601	LIPES ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27,28,30,31,60,61,64-74,79-83 and 86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,28,30,31,60,61,64-73,79-83 and 86* is/are rejected.

7)☒ Claim(s) *74* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed August 13, 2003 has been entered. Claims 27, 28, 31, 64, and 80 have been amended. Claims 29, 32-38, 62-63, 74-77, and 83-84 have been cancelled.

Accordingly, Claims 27, 28, 30, 31, 60, 61, 64-73, 78-82, and 85 are pending in the instant application.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

The second instance of Claim 66 has been renumbered as Claim 67. Misnumbered claims 67-85 have been renumbered 68-86, respectively.After renumbering the claims, Claims 27, 28, 30, 31, 60, 61, 64-74, 79-83, and 86 are pending in the instant application.

Applicants are required to correct the claim dependencies as appropriate.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art

to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 27, 28, 30, 31, 60, 61, 64-73, 79-83, and 86 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants are referred to the final guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, Number 4, pp. 1099-1111 (also available at www.uspto.gov).

Applicants are reminded that the written description requirement is severable from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), *cert.* denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (While acknowledging that some of its cases concerning the written description requirement and the enablement requirement are confusing, the Federal Circuit reaffirmed that under 35 U.S.C. 112, first paragraph, thewritten description requirement is separate and distinct from the enablement requirement and gave an example thereof.). An invention may be described without the disclosure being enabling (e.g., a chemical compound for which there is no disclosed or apparent method of making), and a disclosure could be enabling without describing the invention (e.g., a specification describing a method of making and using a paint composition made of functionally defined ingredients within broad ranges would be enabling for formulations falling within the description but would not describe any specific formulation). See *In re Armbruster*, 512 F.2d 676, 677, 185 USPQ 152, 153 (CCPA 1975).

The claims are directed to a method of producing insulin in a subject *in vivo* by introducing into the subject an intermediate lobe pituitary cell comprising a nucleic acid encoding insulin, wherein said nucleic acid is operatively linked to a heterologous control region.

The claims recite a heterologous control region. At a minimum the heterologous control region must include a promoter that is active in intermediate lobe (IL) pituitary cells to drive expression of the insulin gene. However, the specification only discloses a single promoter that is active in intermediate lobe pituitary cells, i.e. the pro-opiomelanocortin (POMC) promoter. The promoter is an essential element of the claimed invention, but the specification does not describe a representative number of species of promoters that are active in IL cells. Thus, one of skill in the art could not envision the entire genus of promoters that are active in IL cells and consequently, the written description requirement has not been met. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, only a single promoter, the POMC promoter, has been described by its complete structure. However, the claims cover the use of a genus of promoters that are active in IL cells. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In this case, no other species have been described by other relevant identifying characteristics, such as a core structure responsible for IL cell permissive promoter activity. This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of promoters active in IL cells other than the POMC promoter, at the time the application was filed. Thus, it is concluded that the written description requirement is not satisfied for the genus of heterologous control regions recited in the claims.

Enablement

Claims 27, 28, 30, 31, 60, 61, 64-73, 79-83, and 86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing insulin in a subject *in vivo* by introducing into the subject an intermediate lobe pituitary cell comprising a nucleic acid encoding insulin, wherein said nucleic acid is operatively linked to a heterologous control region that

includes the pro-opiomelanocortin (POMC) promoter, does not reasonably provide enablement for the use of cells having other genetic modifications and other promoters. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method of producing insulin in a subject *in vivo* by introducing into the subject an intermediate lobe pituitary cell comprising a nucleic acid encoding insulin, wherein said nucleic acid is operatively linked to a heterologous control region.

The specification discloses transgenic NOD mice that carry a transgene encoding proinsulin under the control of the POMC promoter. The transgenic intermediate lobe pituitaries were transplanted under the kidney capsule of spontaneously diabetic NOD mice. Transplantation resulted in significant weight gain and in the complete remission of diabetic symptoms (page 26, line 11). The grafts showed no evidence of lymphocytic infiltration. At page 26, lines 23-24, the specification discloses that the great majority of insulin secreted by the transgenic pituitaries is fully processed, mature insulin.

The specification fails to provide an enabling disclosure for the use of transgene constructs that do not encode insulin or do not include the POMC promoter because the proper regulation of insulin secretion is critical for successfully carrying out the claimed method. While the specification discusses a variety of strategies for providing glucose-stimulated insulin secretion (e.g. by further providing transgenes that encode glucokinase, ion channels that mediate glucose-stimulated insulin release, GLP-1, and/or GLUT-2) , specific guidance for actually achieving regulated insulin secretion is not provided to the skilled artisan. Achieving glucose-stimulated insulin secretion has been problematic in the art of ex vivo gene therapy and cell replacement therapy for diabetes. Halban et al. (2001) emphasize that the β-cell is remarkably sophisticated and that therapeutic strategies that use surrogate cells will have a number of hurdles to overcome to faithfully mimic the properties of this highly differentiated secretory cell (see abstract). The authors state that insulin is "normally secreted in a well-regulated fashion in rapid response

to the metabolic needs of the individual and most specifically (but not exclusively) to changes in circulating levels of glucose" (abstract). The reference discusses the numerous hurdles that have been encountered in the development of therapeutic strategies that rely on gene therapy or cell-replacement therapy. The authors conclude that "it will be essential to have well-regulated insulin secretion" (page 2189, column 2, paragraph 2) and that "[i]ntroducing glucose-sensitivity to otherwise insensitive cells may be more complex than previously imagined" (page 2189, column 2, paragraph 2).

Xu et al. (2003) discuss the challenges to coupling the synthesis and release of the transgene insulin to serum glucose concentrations. The authors state that "[u]nlike gene therapy for hemophilia ... diabetes gene therapy is much more complicated, as this involves not only insulin generation, but also its modification and release. Insulin is of vital importance in maintaining glucose homeostasis, and its unique role as the only anabolic peptide hormone necessitates strict regulation and fast-acting mechanisms to guarantee efficient insulin biosynthesis and secretion ... A major impediment to sucessful insulin gene therapy has been the difficulty in coupling the synthesis and release of the transgene insulin to serum glucose concentrations. This tight coupling between glucose stimulation and insulin secretion has become the objective of paramount importance to most researchers" (page 73, column 1, paragraph 2). The reference further emphasizes that the ideal surrogate cells would possess the came characteristics as the β cells including (i) glucose-dependent proinsulin gene transcription, (ii) proinsulin proteolytic processing, and (iii) glucose-dependent insulin secretion (page 71, column 1, paragraph 3).

Welsh (2000) provides a discussion of the prospects for gene therapy of diabetes mellitus that agrees with the analysis of Xu et al. (2003) and Halban et al. (2001) regarding the state of the art. Welsh points out that tight control of insulin release is essential to any therapeutic strategy. In discussing *ex vivo* gene therapy experiments and the various cell types used, Welsh states that "[u]nfortunately none of these cells respond to glucose with physiological secretion of insulin. Instead, it is only possible to achieve regulation of insulin gene transcription by using promoter constructs that respond to glucose. Because

transcription is a much slower process that regulated release from secretory granules, there is a substantial risk of the insulin production getting out of phase with fluctuations in glucose levels leading to episodes of severe hypoglycemia. Thus, the generation of a substitute β cell from non-β cells may prove to be exceedingly difficult" (page 181, column 1, paragraph 2).

Given the limited working examples and limited specific guidance for achieving regulated insulin secretion over the broad context of the claims, and further given the unpredictability in the art of ex vivo gene therapy for diabetes, one skilled in the art would have been required to engage in undue experimentation in order to practice the claimed method over the full scope.

Allowable Subject Matter

Claim 74 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, William Phillips, whose telephone number is (703) 305-3482.

Anne-Marie Falk, Ph.D.

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER